

EFFICACY OF ISOTRETINOIN IN ACNE VULGARIS

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Abstract : Isotretinoin was first introduced in India just over 5 years back. In this prospective study, efficacy and side effects of isotretinoin are evaluated in Indian subjects managed in a mid sized service hospital. Cases of nodulocystic acne, therapy resistant severe acne received 0.5 mg of isotretinoin per kg per day for a period ranging from 4 to 10 weeks, a total mean cumulative does of 24.2 mg per kg. A total of 14 subjects were treated with isotretinoin 12(86%) patients achieved the therapeutic goal and 2 (14%) had poor compliance or significant side effects forcing their withdrawal from the study. Adverse effects occurred in all the patients, but led to discontinuation of the drug in only one case. The clinical side effects were similar to those reported in literature except for minor differences in prevalence. Elevation of plasma triglyceride levels was the most significant laboratory adverse effect. The drug induced prolonged remission of active acne from lesions occurred in all cases that completed the therapy.

INTRODUCTION

Acne vulgaris is a common skin disease affecting nearly 80 percent of all people between the age of 11 and 30 years¹. Increased sebum production abnormal keratinization, Propionibacterium acne proliferation and inflammation affect the pilosebaceous follicles especially on the face, neck and upper trunk². Most cases are mild but it can persist and result in disfigurement and permanent and permanent scarring in over 50% of cases³. It is often associated with serious adverse effects on psycho-social development resulting in emotional stress, withdrawal from society and depression⁴. Modes of treatment include topical anti inflammatory and peeling agents, oral and topical antibiotics, hormonal agonists antagonists⁵. The introduction of 13 cis retinoic acid or isotretinoin has revolutionized the management severe cases of can to routine treatment. Isotretinoin is a synthetic vitamin A analogue belonging to the class of retinoids. Isotretinoin is the only drug that acts on all the pathogenic factors of acne. It was first used to treat severe recalcitrant nodulocystic acne and has gradually been accepted for other forms of severe acne as well⁶ It has recently been launched in India and we report our experience with this drug in the Armed forces in the Indian setting.

MATERIAL AND METHODS

In this prospective study, 14 subjects treated with Isotretinoin at MH Secunderabad were evaluated. The aim of the study was to establish the place of Isotretinoin in the treatment of acne and to note its clinical and laboratory side effect in our setting. Inclusion criteria were a) severe nodulocystic acne b) fulminas c) acne resistant to conventional therapy. All subjects were subjected to detailed clinical assessment including details of earlier therapy and advised removal of provocative / aggravating factors (Table 1). The drug was administered in the standard dose of 0.5 mg / kg body wt vis 20-40 mg / day as OD/BD schedule with meals rounded off to the nearest available preparation⁷. Topical antibiotics were the only other medications used during Isotretinoin therapy. The end point of therapy was reduction of more than 80% inflammatory lesions, a total cumulative does of 120 mg / kg body wt or side effects warranting stoppage of the drug.

Relevant hematological and biochemical investigations were done prior to the Institution of the drug and after completion of therapy. Subjects were assessed at 1-2 weeks interval while on therapy and at 2-4 week intervals after completion of the treatment. Patients were cautioned about the side effects of the therapy and asked to report back immediately if they developed any untoward problem. Women of child bearing age were warned against conceiving and advised suitable contraceptive measures prior to initiation of therapy, during treatment and for one month after

completion.

RESULTS

Twelve (12) of the 14 subjects were males with mean age of 21 years. All subjects had received conventional therapy earlier in the form of doxycycline and topical erythromycin / clindamycin or benzoyl peroxide / retinoic acid.

Table-1: Patient profile and Indication of Isotretinoin Therapy

S.No.	Age	Sex	Diagnosis	Previous Therapy
1	17	M	Resistant Acne	Doxycylice+Tretinoin Gel
2	24	M	Resistant Ac	Doxycylice+Tretinoin Gel
3	19	M	Resistant Ac	Doxycylice+Tretinoin Gel
4	16	M	Nodulocystic Acne	Mino cycline+Adalplene Gel
5	18	M	Nodulocystic Acne	Mino cycline+Adalplene Gel
6	25	M	Resistant Ac	Doxycylice+Tretinoin Gel
7	26	M	Nodulocystic Acne	Mino cycline+Adalplene Gel
8	22	M	Resistant Ac	Doxycylice+Tretinoin Gel
9	21	M	Resistant Ac	Doxycylice+Tretinoin Gel
10	22	M	Resistant Ac	Doxycylice+Tretinoin Gel
11	18	M	Resistant Ac	Doxycylice+Tretinoin Gel
12	17	M	Acne Fulminans	Minocycline / Amoxycillin/Clarithromycin+ clindamycin / Benzoyl peroxide Gel
13	31	F	Nodulocystic Acne	Mino Cycline + Oral Contraceptive + Adalplene Gel
14	18	F	Resistant Ac	Dopxycline + Tretinoin Gel

Response to therapy was seen in all patients after 2-3 weeks. Decreased oiliness of skin due to reduction of sebum was the first change. Pustules and papules decreased in a few weeks with decrease in appearance of new lesions and diminution of existing lesions. 2 subjects were required to be administered the drug for 4 weeks, 8 for 6 weeks and 1 for 8 weeks depending on the clinical response. The maximum duration of therapy was 10 weeks in one patient. The drug was stopped in one subject after one week as compliance could not be assured. In our study, on an average isotretinoin was required to be taken for just over 6 weeks to achieve good therapeutic results. The cumulative does in the majority of cases was only 15-35 (mean 24.2) mg/kg much below our initial anticipation. Improvement continued after stoppage of the drug establishing an overall response of 86% of our patients reaching the end point of our therapeutic goal (table 2) An occasional fresh papule appeared especially after stopping therapy in most subjects but regressed spontaneously or with topical erythromycin / clindamycin or benzoyl peroxide. None of the subjects required a second course of isotretinoin in a follow up period of 6 months -11/2 years.

Table 2 Clinical Effects of Isotretinoin Therapy

S.No.	Isotretinoin dose (mg / d)	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	Duration of therapy (weeks)
1	30	Dryness	Lesions Reduced*	Lesions Reduced*			04
2	40	"	No new Lesions				06
3	30	"	Lesions Reduced*				04
4	30	"	No new Lesions	Lesions Reduced*06			06
5	30	"	No new Lesions	Lesions Reduced*06			06
6	40	"	Dryness	Lesions Reduced*			06
7	30	"	Poor compliance therapy stopped				01
8	40	"	Increased Triglycerides – therapy stopped				02
9	30	"	No new Lesions	Lesions Reduced*			06
10	30	"	No new Lesions	Lesions Reduced*			06
11	30	"	No new Lesions	Lesions Reduced*	Lesions Reduced*		08
12	30	"	Dryness	No new lesions	Lesions Reduced*	Lesions Reduced*	10
13	30	"	No new Lesions	Lesions Reduced*			06
14	20	"	No new Lesions	Lesions Reduced*			06

*End point reached

Cheilitis of varying degree was observed in all subjects. 12 to 14 subjects developed dryness of face and lips within 2 weeks of drug therapy. 2 of these 12 patients developed xerostomia. All subject required petrolatum application on the lips after the first few weeks of therapy and was recommended to all subject as a routine. Side effects observed with lesser frequency were palmoplantar desquamation headache photophobia and arthralgia¹. Blood counts were within normal limits in all subjects. Serum triglycerides were raised in 1 subject (450 mg dl) 2 weeks after initiation of therapy which led to discontinuation of the drug (Table 3). The effect of the drug at is 8 weeks after stopping the drug some of the earlier cases prolonged effect on a follow up of one to one and a half years (Table 4).

Table 3: Side Effects of Isotretinoin Therapy

S.No.	Cumulative dose (mg / kg body wt)	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks
1	16.0	Cheilitis	Cheilitis / Xerostomia	Cheilitis / Dryness	Cheilitis / Dryness	Regressed
2	25.0	Cheilitis	Cheilitis	Controlled with Petrolatum	Regressed	Regressed
3	17.0	Cheilitis	Cheilitis	Regressed		
4	24.2	Cheilitis	Palmoplantar desquamation	Controlled with Petrolatum	Controlled with Petrolatum	Regressed
5	21.0	Cheilitis	Dryness	Dryness	Dryness	Controlled with Petrolatum
6	24.0	-	Cheilitis / Dryness	Xerostomia	Regressed	
7	Poor compliance	-	Therapy stopped	-	-	-
8	07.4	Increased Tr.	Therapy stopped			
9	23.3	Dryness / cheilitis	Photophobia	Regressed		
10	23.3	Dryness / cheilitis	Cheilitis	Regressed		
11	30.2	Dryness / cheilitis	Headache	Palmoplantar desquamation	Dryness / cheilitis	Regressed
12	35.0	-	Dryness	cheilitis	Palmoplantar desquamation	Dryness / cheilitis
13	27.0	Dryness	Arthralgia	Arthralgia	Regressed	
14	24.0	cheilitis	Dryness	Headache	Regressed	

Table 4: Follow up of Isotretinoin Therapy

S.No.	3 months	6 months	9 months	12 months	15 months	18 months
1	No fresh lesions	Occ fresh lesion	Occ fresh lesion*		Occ fresh lesion	Occ fresh lesion*
2	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion		
3	No fresh lesions	Occ fresh lesion	Occ fresh lesion*			
4	"	Occ fresh lesion		Occ fresh lesion		
5	"	Occ fresh lesion*				
6	Occ fresh lesion	Occ fresh lesion*				
7	No follow up withdrawn from study					
8	No follow up withdrawn from study					
9	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*
10	No fresh lesions	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*	
11	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*
12	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*	
13	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion	Occ fresh lesion*		
14	No fresh lesions	Occ fresh lesion	Occ fresh lesion*			

* follow up lost thereafter

DISCUSSION

Of all the therapeutic modalities now available only isotretinoin alters the natural course of the disease. It reduces the sebum secretion and this effect persists long after stopping the drug. Prolonged remission has been noted after isotretinoin therapy

Isotretinoin therapy was only initiated in the most recalcitrant cases of acne. An excellent to good response was observed in all our subject. Some of our earlier disillusioned cases dramatically improved with this modality. The cumulative does in the majority of cases was only 15-35 (mean 24.2) mg/kg much below the recommended schedule^{7,8}. Peak improvement was seen at 4-8 weeks after cessation of therapy. The efficacy persisted fairly long after stopping the drug. Our earliest cases continued to sustain the effects even more than one and a half years after stopping the drug. This outcome is not observed with any other treatment and also decreases the total cost of therapy. Initial literature gives a long term remission rate of 61% at the end of nine years with only 23% requiring a second course of therapy. It is difficult to predict the future requirement of a course of isotretinoin as factors related to relapse include long duration of complaints, presence of severe truncal acne, and is higher in females older than 25 years. Higher relapse rates are also noted to be within the first 3 years and patients administered isotretinoin < 0.5 mg/kg per day or cumulative does < 120 mg / kg Recently prospective studies have shown isotretinoin to be equally effective in lower doses in combination with other topical / systematic drugs Intermittent isotretinoin therapy has also emerged as a viable alternative to control milder forms or relapses in acne¹¹ Unfortunately follow up in our patients was only possible for an over a year on an average inadequate to clearly envisage the future requirements of isotretinoin. However, our results are in accordance with current recommendations of low dose isotretinoin therapy to avoid its side effects.¹² No significant side effects were noted in any of our patients. Xerosis and cheilitis are extensions of the therapeutic effects of the drug and were easily controlled by moisturizing agents. These were corresponding to those mentioned in literature being limited to skin and mucus membranes. Metabolic changes and arthralgia were detected early and reversed on stopping therapy. The risk benefit ratio was clearly in favour of our patients in view of the low total dose, male sex predominance and short duration of therapy.

It is thus concluded that isotretinoin is a safe and highly effective therapy, capable of producing remission in severe forms of acne. However, its optimum dose and ideal therapeutic regimen scheme are still under discussion and many long follow up studies in different groups of patients would finally decide the best schedule for long remissions with the least adverse effects.

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